

## The Effects of Halothane on Sympathetic Ganglionic Transmission

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The effects of halothane on ganglionic transmission were studied in the stellate ganglion of the guinea pig using intracellular recordings *in vitro*. Depression of synaptic transmission is one of the actions common to many general anesthetics. The aim of this study was to investigate which of the processes involved in synaptic transmission are affected by halothane in concentrations comparable to those used during surgical anesthesia. The neurons of the stellate ganglion were depolarized using preganglionic nerve stimulation, postganglionic nerve stimulation, and intracellular stimulation before and after introduction of halothane (vaporizer settings of 0.75% and 1.5% produced bath concentrations of 8 and 18 mg/dl, respectively). Halothane at both concentrations depressed sympathetic ganglionic transmission which was induced by stimulation of preganglionic nerves. Axonal transmission and the excitability of the postganglionic neurons to direct intracellular stimulation was far less sensitive to halothane than synaptic transmission. The depression of ganglionic transmission seen in the present study was most likely due to a decrease in transmitter release although alterations in postsynaptic receptor properties could have been involved as well. The decrease in sympathetic activity resulting from depression of ganglionic transmission probably contributes to the arterial hypotension seen during halothane anesthesia, along with direct myocardial depression, inhibition of catecholamine release from the adrenal medulla, direct action on vascular smooth muscle, and central sympathetic depression. (Key words: Anesthetics, volatile: halothane. Membrane: cell. Nerve: membrane. Sympathetic nervous system: anesthesia; ganglionic transmission.)

IN 1906, SHERRINGTON<sup>1</sup> attributed the depression of reflexes by anesthetics to their action on synaptic transmission rather than to their effect on the conduction of nerve impulses along nerve trunks. The more recent investigation of Larrabee and Posternak<sup>2</sup> showed that synaptic transmission through sympathetic ganglia is suppressed by anesthetics (chloroform, ether, and sodium pentobarbital) at lower concentrations than those required to block conduction of impulses along nerve fibers. This indicates that synaptic block occurs at concentrations of anesthetics which are lower than those

required to inhibit metabolism and oxygen consumption.<sup>3</sup> The evidence in favor of such a hypothesis has been reviewed.<sup>4,5</sup>

The effects of halothane on ganglionic transmission have been studied using a variety of methods.<sup>6-14</sup> The depressant effects of halothane on synaptic transmission are of interest, not only because the ganglionic effects of this agent may contribute to its overall influence on autonomic function,<sup>10,15-19</sup> but also because the effects of halothane on the central nervous system probably involve synaptic processes.<sup>8,13</sup> It has been suggested that halothane depresses ganglionic transmission that involves muscarinic receptors as well as transmission that involves nicotinic receptors.<sup>12</sup>

Much of our present knowledge of cellular effects of volatile anesthetics comes from intracellular studies on the giant neurons of *Helix*, *Aplysia* and *Sepia*.<sup>8</sup> Electrophysiologic studies of the effect of halothane on mammalian autonomic ganglia have been confined mainly to extracellular recordings. From the available data, the site of action of halothane within the ganglion remains obscure. Possible sites are: conduction of nerve impulses along the nerve fibers, direct effects on the postsynaptic neuron, and neurotransmitter release.

The present study was designed to address the following question: Which of the processes involved in sympathetic ganglionic transmission are affected during halothane anesthesia? For this purpose the effects of halothane on the following processes of synaptic transmission were tested: 1) the conduction of impulses along the nerve fiber; 2) the excitatory postsynaptic potential (EPSP); and 3) the excitability of the postsynaptic neuron. The action of halothane on each of these processes was tested using intracellular recordings from the neurons of the stellate ganglion of the guinea pig.

### Materials and Methods

Twelve adult guinea pigs of either sex weighing 150 to 250 g were killed by cervical dislocation. The left stellate ganglion, together with short sections of the preganglionic and postganglionic nerves, were rapidly isolated and transferred to an organ bath. The ganglia were superfused with a Krebs's solution of the following composition (in mM): Na<sup>+</sup>, 137; K<sup>+</sup>, 5.9; Ca<sup>++</sup>, 2.5; Mg<sup>++</sup>, 1.2; Cl<sup>-</sup>, 134; HCO<sub>3</sub><sup>-</sup>, 15.5; H<sub>2</sub>PO<sub>4</sub><sup>-</sup>, 1.2; and glucose, 11.5. The solution was equilibrated with 97% O<sub>2</sub> and 3% CO<sub>2</sub> and maintained at 37° C and pH 7.40

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Received from the Departments of Anesthesiology, Physiology, and Pathology, The Medical College of Wisconsin, Milwaukee, Wisconsin. Accepted for publication May 20, 1982. Supported by the National Heart and Lung Institute (Grant GM 29641-01) and the Medical Research Service of the Veterans Administration. Presented in part at the annual meeting of the American Society of Anesthesiologists, October 1981.

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$\pm 0.05$ . The preparation was pinned to a transparent silastic rubber floor (Sylgard-Dow Corning) using fine (25- $\mu\text{m}$ ) tungsten wire pins, and was superfused continuously at a rate of 15 ml/min. With the aid of a dissecting microscope, the connective and fibrous tissue located on the top of the stellate ganglion were removed. The preganglionic (T3 ramus) and postganglionic nerves (ventral and dorsal ansae subclavia) were desheathed and placed on bipolar tungsten electrodes for stimulation. These tungsten electrodes were connected to stimulator isolation units (WP Instruments). Electrical stimulation of the nerves was produced by rectangular monophasic pulses of 1.0-ms duration, 1 Hz, at a constant current of up to 15 mA. The current used was dependent upon the size of the nerve trunk and the amount of adherent connective tissue. Current strengths were selected to produce subthreshold potentials (fast excitatory postsynaptic potentials), threshold potentials, and supra-threshold potentials, as measured with intracellular recordings. Effects of halothane (Ayerst Laboratories) on responses of the stellate ganglion neurons were tested simultaneously during antidromic stimulation followed by orthodromic stimulation whenever possible. Excitability of the neurons also was tested by direct stimulation of the neurons with a depolarizing pulse (100  $\mu\text{s}$ ) applied through the recording microelectrode. Current strength was increased gradually until a single action potential was consistently evoked. Current thresholds for the production of an action potential ranged between  $1-5 \times 10^{-9}$  A, and once achieved, remained constant throughout the experiment.

The transmembrane potentials were measured by means of short tapered ultra-fine glass microelectrodes, filled with 3 M KCl and with tip resistance of 50 to 80 M $\Omega$ . Electrodes were placed on a holder which was attached to a hydraulic microdrive and micromanipulator. Intracellular potentials were detected by means of an electrometer (WP Instruments, M 707) and a storage oscilloscope (Tektronix R 5113). Electrical activity also was recorded simultaneously on a FM tape recorder (Tandberg Series 100) and displayed on a digital oscilloscope (Nicolet Instrument Corp.) whose output was plotted on an X-Y recorder. The resting membrane potential was measured as the difference in potential when the electrode was deliberately withdrawn from the cell into the bathing solution.

During orthodromic stimulation of the T3 ramus, the spike response in a postsynaptic cell body was preceded by an initial depolarization phase (fast EPSP). Since the ganglion cells were innervated by several preganglionic fibers which differ in threshold, it was possible to adjust the strength of the stimulus to cause a

desirable synaptic response, *e.g.*, subthreshold, threshold, and supra-threshold activity. The threshold for a sudden voltage shift is thought to be the value of membrane potential at which the instantaneous inward sodium current is large enough to balance the instantaneous outward potassium current. On one side of that voltage, the potassium current will dominate and a spike will not occur, but EPSPs will still be present (subthreshold stimulation), and on the other side, the sodium current will dominate, leading to an action potential (threshold stimulation).

In order to determine whether the conduction of impulses along the axon was impaired by halothane at similar concentrations to those required to block synaptic transmission, antidromic stimulation was performed. The term antidromic indicates a direction opposite to the normal direction of impulse propagation along nerve fibers. The conduction velocity of antidromic nerve impulses along nerve fibers is the same as the conduction velocity of impulses propagated in an orthodromic direction. Antidromic conduction can be elicited by electrical stimulation, thereby providing an easy way of identifying the projection of a neuron and the conduction velocity of impulses along its axon. Activation of the cell body by antidromic stimulation is independent of synaptic mechanisms. When an antidromic impulse is propagated into a ganglion cell (*e.g.*, stimulation of dorsal ansa subclavia), it results in an action potential with a sharp rising phase (no fast EPSP) and a relatively slow falling phase, followed by a long-lasting after-hyperpolarization. The size and time course of spike potentials evoked by direct intracellular stimulation were similar to those elicited by an antidromic impulse.

Resting membrane potentials ranged from  $-52$  to  $-70$  mV. Halothane was introduced by switching to superfusate equilibrated for at least 10 min with halothane (Dräger vaporizer) at the rate of 2 l/min. The concentration of anesthetic in the bath was measured by a gas chromatograph using a flame ionization detector. Vaporizer settings of 0.75% and 1.5% corresponded to concentrations of 8 and 18 mg/dl in the bath, respectively. Only data from impalements of the neurons which had stable resting membrane potentials and were maintained through the control, experimental, and recovery periods were included in this study. Successful observations with stable membrane potentials before and after exposure to halothane from seven ganglion preparations (an average of six cells per ganglion) were used for statistical analysis. Data were analyzed by two-way analysis of variance. Scheffe's test was used to analyze differences between treatment means. Probabilities of  $< 0.05$  were considered significant.

**Results**

**SUBTHRESHOLD STIMULATION  
(28 CELLS, SEVEN GANGLIA)**

Subthreshold orthodromic stimulation (T3 ramus) during the control period is seen in figure 1A. After five minutes of 0.75% halothane (fig. 1B), and 1.5% halothane (fig. 1C), the slopes of the EPSPs and their absolute magnitude were reduced. Table 1 summarizes 131 observations from seven ganglionic preparations during 0.75% and 1.5% halothane. The reduction of the EPSP amplitude was significant between all conditions.

**THRESHOLD STIMULATION  
(35 CELLS, SEVEN GANGLIA)**

Intracellular activity of stellate ganglion cells was tested during both antidromic stimulation and orthodromic stimulation (fig. 2). As shown in these tracings, the effect of stimulation of the dorsal ansa (antidromic stimulation) was not affected after introduction of 1.5% halothane. Electrical stimulation of the T3 ramus (threshold orthodromic stimulation) produced an action potential during the control, and only an EPSP after five minutes of exposure to 1.5% halothane. Therefore, the conduction of impulses along postganglionic axons (DA-stimulation) was not affected (table 1) at concentrations of halothane required for the maintenance of general anesthesia, while synaptic transmission was depressed, and action potentials were eliminated. Failure to conduct action potentials evoked by threshold stimulation after five minutes of exposure to 0.75% halothane was observed in 33 of 35 cells, while 5 min of exposure to 1.5% halothane eliminated all action potentials (35 of 35 cells).

It was also possible to obtain synaptic input while stimulating some postganglionic nerves in three ganglion preparations. It has been shown that the neurons of the stellate ganglion receive excitatory synaptic input from axons originating from receptors in the cardio-

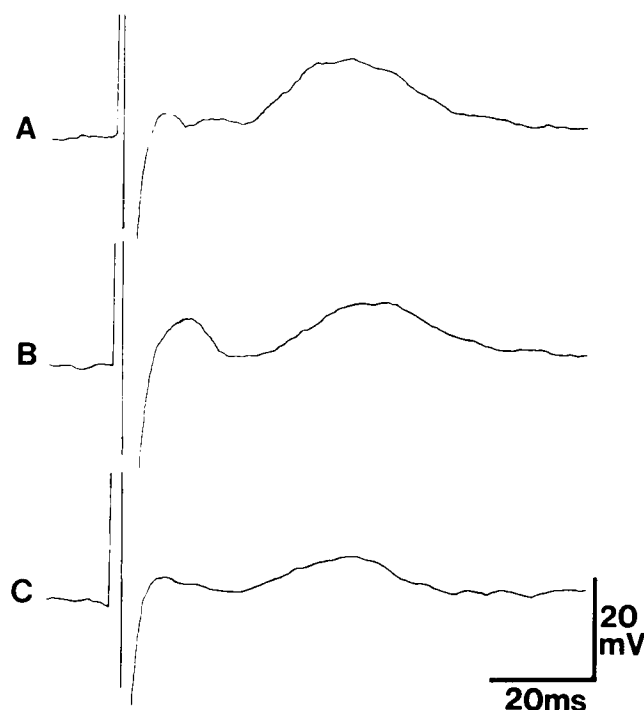


FIG. 1. Intracellular responses to subthreshold orthodromic stimulation (T3 ramus) during the control (A), 0.75% halothane (B), and 1.5% halothane (C). The slope of the EPSPs and their absolute magnitudes were reduced.

pulmonary region.<sup>20,21</sup> Figure 3 shows an example of synaptic input (fast EPSPs) from both the T3 ramus and the dorsal ansa (control- at threshold stimulation). After introduction of halothane (1.5%) a progressive effect of the anesthetic is seen on synaptic transmission. The action potentials were eliminated and the EPSPs were depressed gradually. After five minutes of washout, ganglionic transmission returned to the control.

**SUPRATHRESHOLD STIMULATION  
(19 CELLS, FOUR GANGLIA)**

Supramaximal electrical stimulation (four times threshold) of the preganglionic input (T3 ramus) also

TABLE 1. Effects of Halothane on Cellular Responses

	Subthreshold Stimulation (EPSP)		Suprathreshold Stimulation after Spike Hyperpolarization (mV) (19)	Resting Membrane Potential (mV) (28)	Conduction Velocity (m/s) (28)
	(28) Amplitude (mV)	(28) Slope (V/s)			
Control	11.47 ± 0.8	1.74 ± 0.56	11.8 ± 1.5	61.8 ± 2.9	1.02 ± 0.11
0.75% Halothane (8 mg/dl)	7.76 ± 0.4†	1.08 ± 0.36*	8.2 ± 0.9	62.6 ± 2.8	0.98 ± 0.09
1.5% Halothane (18 mg/dl)	4.52 ± 0.5†,‡	0.72 ± 0.27*	5.2 ± 0.9*	61.6 ± 2.9	1.04 ± 0.1

Number of observations in parentheses.  
Values are means ± SEM.  
\* P < 0.05 vs. control.

† P < 0.01 vs. control.  
‡ P < 0.01 vs. 0.75% halothane.

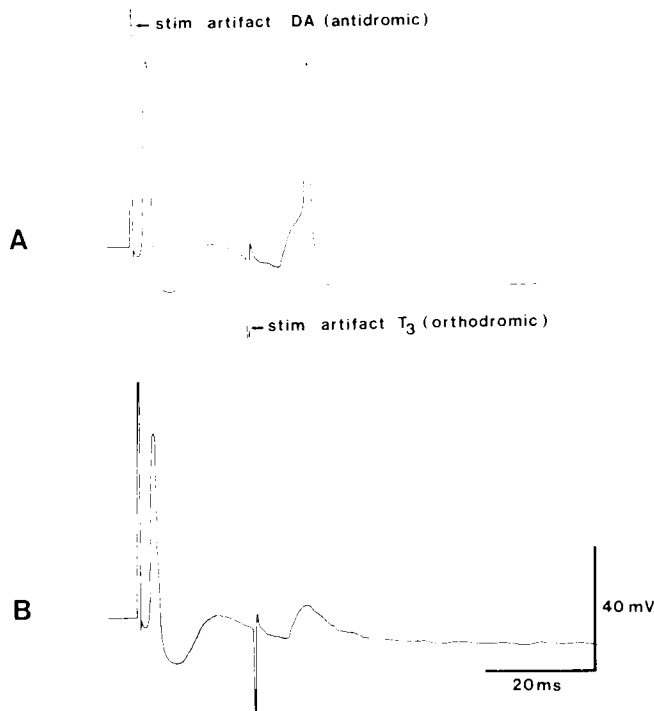


FIG. 2. Intracellular responses of the stellate ganglion neuron were tested during antidromic stimulation of the dorsal ansa (DA) followed by orthodromic stimulation of the T3 ramus (T3), during the control (A), and after introduction of 1.5% halothane (B).

was performed in four ganglion preparations. Example of such stimulation is shown in figure 4, during the control (fig. 4A), after 0.75% halothane (fig. 4B), and after 1.5% halothane (fig. 4C). These concentrations of halothane did not eliminate evoked potentials in 19 ganglion cells studied, although decreases in the after hyperpolarization of the action potential were seen (table 1).

#### INTRACELLULAR STIMULATION (19 CELLS, SIX GANGLIA)

The effects of halothane on changes in direct excitability were tested by applying threshold depolarizing pulses through the recording microelectrode. Short lasting intracellular depolarizing stimulation at threshold is seen in figure 5-1C, following orthodromic threshold stimulation of the T3 ramus during control (fig. 5A), and after five minutes of 1.5% halothane (fig. 5B). Synaptic ganglionic transmission was affected as shown by the elimination of the action potential. Under these experimental conditions, the threshold required for direct intracellular depolarization of the neuron was not increased after 1.5% halothane in the 19 cells studied.

#### Discussion

The vertebrate sympathetic ganglia usually respond to preganglionic stimuli with three types of postsynaptic potentials in the following order: an initial fast excitatory postsynaptic potential (f-EPSP), a slow inhibitory postsynaptic potential (s-IPSP), and a slow excitatory postsynaptic potential (s-EPSP).<sup>22-25</sup> The f-EPSP is mediated by a nicotinic acetylcholine receptor and the s-EPSP by a muscarinic acetylcholine receptor. The synaptic pathway of the s-IPSP may include adrenergic cells which release a catecholamine transmitter in response to the muscarinic action of acetylcholine, which in turn hyperpolarizes the ganglion cell. Other hypotheses, including a possible role of cyclic AMP for the s-IPSP, have been reviewed recently.<sup>26</sup>

We have studied the effects of halothane on the fast

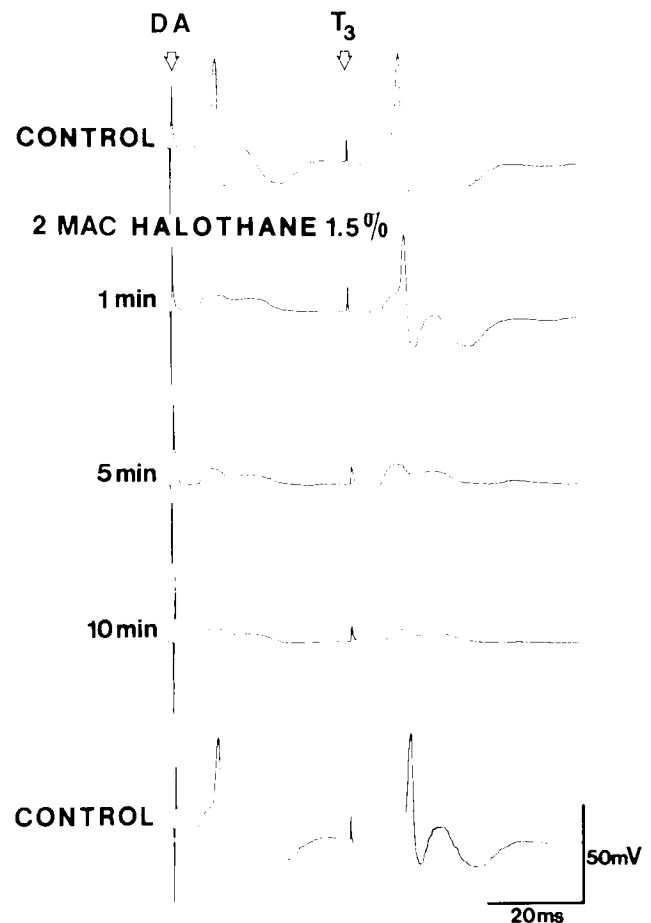


FIG. 3. Action potentials were recorded from the cell body of a postganglionic neuron in the stellate ganglion after threshold stimulation of the dorsal ansa (DA) and the T3 ramus (control). Introduction of 1.5% halothane eliminated the action potential and further exposure also decreased the amplitude of the EPSPs.

EPSPs, the conduction of action potentials along the nerve fibers, and the excitability of the nerve cells. The fast EPSP has a rapid time course and plays a primary role in ganglionic transmission.<sup>22</sup> The characteristics of the action potentials and conduction velocities of the postganglionic fibers reported in this study were compatible with those described in the literature for the guinea pig inferior mesenteric ganglion and the superior cervical ganglion. The resting membrane potential in the sympathetic ganglia of the guinea pig ranges from

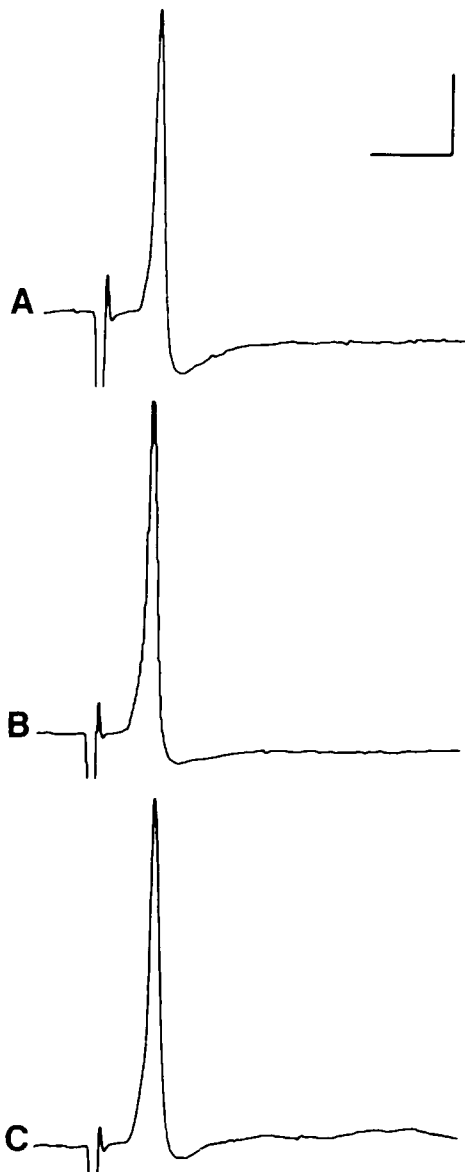


FIG. 4. Intracellular responses to supramaximal orthodromic stimulation (T3 ramus) during control (A), 0.75% halothane (B), and 1.5% halothane (C). The action potential was not eliminated even at prolonged exposure to 1.5% halothane. Calibration: 10 ms, 20 mV.

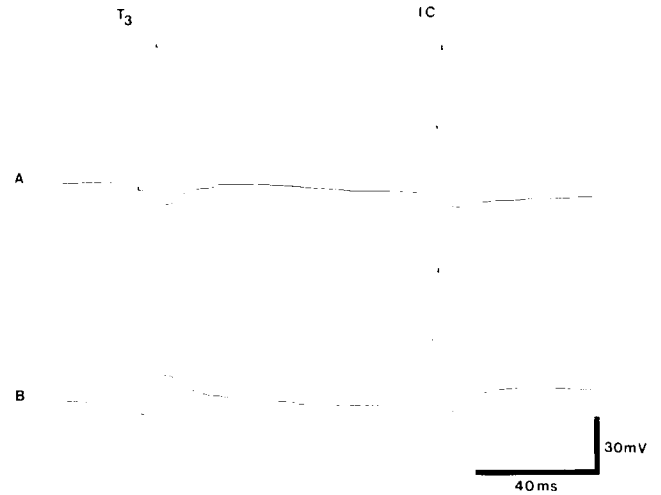


FIG. 5. Intracellular responses to orthodromic threshold stimulation at the T3 ramus is followed by the threshold intracellular depolarizing stimulation (IC), during the control (A), and after five minutes of 1.5% halothane (B). Synaptic transmission was eliminated without changes in the threshold depolarization required for action potential generation in the cell body.

-40 to -70 mV, which is less than that in the spinal motor neurons.<sup>27,28</sup> The differences are probably due to the smaller size of the neuronal cell body (average of 35  $\mu$ m in the sympathetic ganglia *vs.* 70  $\mu$ m in the spinal motor neuron).<sup>27</sup> The conduction velocities of the postganglionic fibers have been reported to range from 0.8–1.0 m/s in the guinea pig.<sup>28</sup>

As indicated earlier, the interruption of synaptic transmission by halothane (or any other agent) could be caused by any one or more of the following possibilities: 1) Halothane interferes with the conduction of nerve impulses along the nerve fibers. Conduction velocity along the postganglionic nerve fibers was not affected by halothane as indicated by antidromically evoked potentials. Therefore, the depression of the synaptic potentials by halothane in the concentrations studied was not due to a direct action on the sympathetic nerve fibers. 2) Halothane increases the electrical threshold of the postsynaptic cell. The electrical threshold of the neurons was investigated by threshold intracellular stimulation through the recording electrode. No evidence was found to suggest that halothane had any significant action on threshold depolarization required for the action potential generation at concentrations of halothane that block ganglionic transmission. 3) Halothane interferes with the processes involved in chemical neurotransmission. The experimental results clearly show that fast EPSPs are reduced by halothane. There are at least two mechanisms that could account for the reduction in the EPSP caused by halothane. Halothane could act

directly on the release mechanism to reduce the output of the transmitter to a given presynaptic stimulation or it could reduce the sensitivity of the postsynaptic membrane to the endogenously released transmitter. If halothane does alter the biochemical or biophysical properties of neuronal membranes in the ganglion, and thereby affects the membrane lipoproteins presumably responsible for neurotransmitter binding or cell activation, the sensitivity of the neurons to the neurotransmitter could be altered as well. However, if one assumes that alteration in fluidity of the postsynaptic membrane could also affect the electrical threshold of the cell, this mechanism cannot apply at these concentrations of halothane, since the excitability of the neuron was unaffected. It is conceivable that halothane could interact with membrane receptors without changing the electrical excitability of the neuron, and therefore selectively inhibit receptor activation. In isolated bovine adrenal glands, it has been postulated that halothane causes a conformational change of membrane proteins, associated with nicotinic receptors leading to a decrease in catecholamine release.<sup>29</sup> Other studies concluded that acetylcholine released from hypogastric nerves and splanchnic nerves was depressed by halothane.<sup>30,31</sup> Therefore, it is probable that both mechanisms (presynaptic and receptor site) may contribute to the inhibition of spontaneous catecholamine secretion from the adrenal medulla caused by this anesthetic.

The mechanism responsible for the generation of the slow negative after potential is a matter of controversy.<sup>26</sup> It has been suggested that following orthodromic stimulation, a two-component system is responsible for the generation of the slow after hyperpolarization. The first component is associated with an acceleration of the sodium pump in the ganglion cell membrane, while the second mechanism may be due to activation of a potassium conductance. In addition, it has been proposed that stimulation of adrenergic receptors on the postsynaptic membrane results in antagonism of an inward calcium current which leads to a slow negative after potential. The processes responsible for the afterspike hyperpolarization were found to be inhibited by halothane in the present study.

Several attempts to analyze the mode of action of halothane using intracellular recordings have been made on ganglia in *Aplysia* and *Helix*.<sup>8</sup> These experiments showed that halothane increased the threshold of the postsynaptic cells to synaptic excitation. There seems to be little point in correlating these results in relation to those reported in this paper since their experiments were conducted at low temperatures and the doses of halothane used were almost five times those

required for anesthesia in mammals. It is not clear whether these doses would be anesthetic or lethal for the *Aplysia*. In a more compatible study of the mechanism of halothane anesthesia in the guinea pig,<sup>13</sup> halothane (up to 1.5%) had no effect on the threshold of the nerve fibers to electrical stimulation or on that of the postsynaptic cells to synaptic excitation.

The results of this study, taken together with previous investigations, imply that the most likely site of action of halothane on the sympathetic ganglion is the presynaptic terminal. For the present, it appears that the reduction in transmitter release that is caused by halothane may be due to an action on the release process itself, perhaps interfering with the influx of calcium into the presynaptic terminal. The mechanism of such an effect remains to be elucidated, and further investigations in this direction may be helpful in understanding the CNS nature of the anesthetic state. This study also has indicated that the threshold for direct electrical activation of the ganglion cell does not appear to be inhibited at concentrations of halothane which inhibit synaptic transmission in sympathetic ganglia. On the other hand, an electrical event associated with repolarization (the negative after potential) in sympathetic ganglion cells appears to be inhibited by halothane. The significance of this observation remains to be determined.

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